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Clinical and immunological studies in a case of selective complete Clq deficiency

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SUMMARY

A 10-year-old male with recurrent skin lesions and chronic infections was found to have a selective deficiency of Clq after functional analysis of all complement components. The addition of highly purified human Clq to the patient's serum restored Cl activity, indicating the presence of Clr and Cls and the absence of Clq. Titration of highly purified Clq with patient serum as a source of Clr and Cls resulted in a linear dose-response curve. The undetectable CH50 activity temporarily returned to normal within a few hours of plasma infusion, but the Cl titres were still only 1–3% of normal. Following plasma administration, the peak of Clq activity was reached after 30 min and returned to undetectable levels within 24 hr. The patient serum was not anti-complementary when incubated with normal serum. Nine members of the family, including the parents and two healthy siblings, were subjected to complement studies and HLA typing. The Cl titres and CH50 activity were found to be normal in all except the paternal grandmother who showed reduced levels of all the complement components. There was no linkage for the gene of Clq deficiency and HLA antigens. Among the various laboratory studies performed, anti-smooth muscle antibodies, immune complexes and anti-HBsAg antibody were found to be positive. The child died of a disease compatible with septicaemia. Post mortem tissue studies by light, fluorescent and electron microscopy have shown the presence of a mesangioproliferative glomerulonephritis.

INTRODUCTION

Rapid progress in the studies of complement deficiency states has revealed that they are mostly genetically determined defects and often associated with serious disease. Within the past decade, several selective complement abnormalities have been reported during the course of systemic lupus erythematosus (SLE) and other collagen diseases (Agnello, 1978; Day & Good, 1975). Clq, a subcomponent of the first component of complement, has been observed to be deficient in patients with severe combined immunodeficiency (Ballow *et al.*, 1973; Gewurz *et al.*, 1969; O'Connell *et al.*, 1966), hypogammaglobulinaemia, systemic lupus erythematosus and myeloma (Atkinson *et al.*, 1978; Kohler & Müller-Eberhard, 1972), and in syndromes resembling lupus with various cutaneous manifestations or vasculitis (Marder *et al.*, 1976; McDuffie *et al.*, 1973; Sissons, Williams & Peters, 1974; Wara *et al.*, 1975).

Recently, we encountered a patient with selective deficiency of Clq associated with recurrent skin lesions and chronic infections of the skin, ears and other systems (Berkel *et al.*, 1977; Loos, Thesen & Berkel, 1978). In this communication we present further clinical, genetic and immunological studies on this patient.

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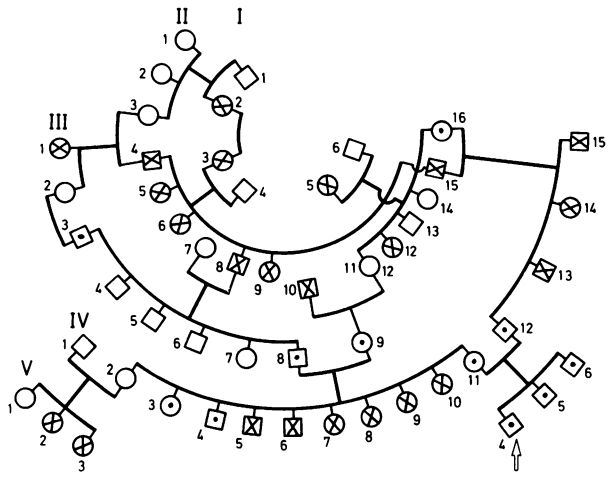

FIG. 1. The family tree. (⊗) Expired, (⊡) investigated.

CASE REPORT

A 10-year-old white male (H.I.I.) was seen at Hacettepe Children's Hospital with fever, vomiting and convulsions which had developed 10 days prior to his admission. Physical examination revealed positive meningeal signs and some hyperkeratotic, desquamative skin and scalp lesions. The peeling of the plantar and palmar regions, hyperpigmented areas measuring about 2×2 cm over the abdomen and extremities, monilial and aphtous lesions of the mouth and soft palate, deformed finger and toe nails with monilia-like lesions and a purulent otitis in the right ear were other positive findings. Purulent meningitis of an undetermined organism was diagnosed and responded to antibiotics, with the return of cerebrospinal fluid and clinical findings to normal at the end of the second week (Berkel *et al.*, 1977). Subsequently, his febrile episodes continued during a period of 5 months spent in hospital. A plasmapheresis was performed in the eleventh week of admission for 3 successive days by exchanging 15 ml of the patient's plasma per kg of body weight with an equivalent volume of fresh frozen plasma. He became afebrile, the skin lesions disappeared and clinically he appeared well after this therapy. However, new lesions developed within 10 days of cessation of the plasmapheresis. He died with a clinical picture compatible with septicaemia despite the use of energetic antibiotic and supportive therapy. Permission for the examination of certain organs by needle necropsy was granted after his death.

The patient's past history revealed an illness characterized by generalized swelling and redness of the body and face shortly after the administration of an antiserum for tetanus following a wound injury at age of 3 years. He was hospitalized for 2 months for peeling and pustular lesions in the skin which developed a week after the therapy. He gradually lost his hair and finger nails which grew again in a deformed manner. The skin lesions would not respond to any systemic or local treatment and were aggravated at times with recurrent peeling in the plantar and palmar areas.

The mother's grandmother and the father's mother were sisters (Fig. 1). Both parents were healthy. The patient (V-4) had two healthy brothers, and no similar illness was described in the family. The patient was the first child, being the product of a normal full-term pregnancy and delivery. Smallpox vaccination and measles were uneventful. The rest of his history was non-contributory.

Laboratory findings

Laboratory studies, including liver and renal function tests, serum electrolytes, phosphorus and zinc, blood and urine aminoacids, ASO, CRP, karyogram, direct Coombs, LE cell, latex and cryoglobulins, isohaemagglutinins, the blastogenic transformation response to phytohaemagglutinin (PHA), candida and allogeneic lymphocytes were within normal values. Delayed hypersensitivity responses detected by four different skin test antigens were negative, and E-rosette values were low (35%) (Berkel *et al.*, 1977).

Urinalysis showed trace to ++ albuminuria with an acid pH and specific gravity of 1·006–1·022. There were between eight and ten leucocytes in the initial urinary sediment which disappeared in the subsequent specimens. The haemoglobin varied between 4·5 and 13·2 gm/dl. The white blood cell count varied between 4000 and 32,400/μl with a predominance of PMN. The absolute lymphocyte count was low (< 2000/μl) on seven occasions, generally varying between 880 and 4900/μl. Serum calcium was 7·4–8·8 mg/dl. Total protein and albumin varied from 5·2 to 6·8 gm/dl and from 1·8 to 3·0 gm/dl. Serum immunoglobulins, determined by radial immunodiffusion (Fahey & McKelvey, 1965) using plates from Behringwerke Company, were within the normal range: IgG, 935 mg/dl; IgM, 162 mg/dl; and IgA, 210 mg/dl. Autoantibody studies* were negative for antinuclear antibody, anti-reticulin and mitochondrial antibodies, but anti-smooth muscle antibodies were bound to be positive. An ante-mortem skin and muscle biopsy disclosed chronic dermatitis and muscle which appeared normal. Examination of the skin with fluorescinated (FITC) monospecific antisera showed a diffuse staining of the dermis with anti-IgG and a granular staining in the basal layers of the epidermis with anti-C3. There was also strong staining with anti-β_1C on the walls of the blood vessels. The following tests were done† in order to eliminate an underlying collagen disease and gave normal results: native DNA (measured by RIA, Amersham), ribonucleoprotein (by counter-immunoelectrophoresis), HBsAg (by RIA, Abbott), HBeAg and anti-HBeAg antibody (by double agar immunodiffusion). Anti-HBsAg antibody (by RIA, Abbott), however, was found to be positive, as were immune complexes by the macrophage test. Complement deficiency was considered because of persistent skin lesions. A CH50 test showed no detectable haemolytic activity. Therefore, the serum was analysed for individual complement components.

MATERIALS AND METHODS

Complement reagents and assays. Blood was allowed to clot for 30 min at room temperature, placed at 4°C for 30 min and then centrifuged for 5 min. The separated serum was kept frozen in small aliquots at −70°C until assayed. Buffers, veronal-buffered saline (VBS) with EDTA or sucrose, a preparation of cell intermediates (EA, EAC$\bar{1}$4 etc.), the CH50 assay and the molecular titration of C1, C4 and C2 have been described previously by Rapp & Borsos (1970). The haemolytic assay for the subcomponent C1q was performed as described by Müller, Hanauske-Abel & Loos (1978). The subcomponents C1r and C1s were quantified by electroimmunoassay and expressed as a percentage of a normal standard pool as described by Sjöholm (1975) and Sjöholm, Martensson & Laurell (1976). Monospecific anti-human C1q was purchased from Behringwerke, Marburg, FRG.

The results of the titrations were expressed as CH50 units/ml or effective molecules/ml (eff. mol/ml), respectively. C$\bar{1}$ was purified by zonal ultracentrifugation according to Colten *et al.* (1969). Functionally pure human and guinea-pig complement components were purchased from the Cordis Corporation, Miami, Florida. Functional assays of the late-acting components were performed as described by Nelson *et al.* (1966), but with slight modification as recommended by the Cordis Corporation. All complement titrations were done using the microlitre modification according to Ringelmann *et al.* (1969).

HLA typing. HLA-A and HLA-B types were determined by using a two-stage microcytotoxicity test (Ray, Hare & Kayhoe, 1973). The tray contained seventy-five antisera to determine thirty-two specificities. The sera were obtained from the serum bank of National Institute of Allergy and Infectious Diseases of the National Institutes of Health.

Tissue studies. Tissues of the skin, muscle, liver and kidney for light microscopy were stained with hematoxylin and eosin (H&E). Staining with H&E, periodic acid-schiff, periodic acid-methenamin silver and Masson's trichrome was carried out on the kidney. For immunofluorescence microscopy, kidney, skin and muscle tissues were snap-frozen in CO_2 and cryostate sections cut 4 μm thick were stained with fluorescein isothiocyanate (FITC) conjugated antisera with anti-human IgG, IgM, IgA, C3, C1q, fibrinogen and HBsAg (Behringwerke) by the direct method. After staining, the tissues were washed in phosphate-buffered saline (PBS, pH−7·2), mounted in buffered glycerol and examined with a Carl-Zeiss Universal fluorescence microscope equipped with a mercury lamp. Fluorescence was graded on a scale from 0 to 4+. For electron microscopy, a small portion of renal biopsy specimen was cut, using double blades, into still smaller pieces in 2% gluteraldehyde in Sorenson buffer, pH 7·2. Tissue blocks were then fixed in the same solution for 4 hr, rinsed in the same buffer, and refixed in 1% osmium tetroxide in Sorenson buffer, pH 7·3, for 2 hr. Embedding and other procedures were done in epoxy resin following the standard techniques. The blocks were sectioned and stained according to previously published methods (Reynolds, 1963; Sato, 1967), and examined on a Carl-Zeiss EM 9 S-2 microscope.

* Kindly performed by Dr E. Gülmezoglu using heterologous tissue and direct immunofluorescence method.

† Kindly performed by Dr and Mrs P. Joller, Kinderspital, Zürich.

TABLE 1. Haemolytic titres of complement components in serum samples of the patient and family members

	V-4	IV-11	IV-12	V-5	V-6	II-16	III-3	III-9	III-8	IV-4	IV-3	NHS* (control
CH50 (u/ml)	0	33·4	40·2	36·3	33·4	0	35·7	40·3	37·8	36·0	35·0	33·8
C1 eff. mol/ml ($\times 10^{-13}$)	0	1·2	1·5	1·4	1·6	0·02	1·3	1·4	1·6	1·4	1·4	1·5
C4 eff. mol/ml ($\times 10^{-12}$)	4·1	2·9	3·3	3·0	2·6	0·0007	2·3	2·8	2·3	2·6	2·0	2·4
C2 eff. mol/ml ($\times 10^{-11}$)	4·0	1·4	1·1	1·4	1·1	0·002	1·6	1·3	1·3	1·2	1·1	1·4
C3 eff. mol/ml ($\times 10^{-11}$)	3·6	1·7	3·0	2·5	3·7	0·4	2·7	2·9	3·1	2·5	3·0	2·9
C6 eff. mol/ml ($\times 10^{-12}$)	4·2											4·0
C7 eff. mol/ml ($\times 10^{-12}$)	6·2											3·5
C8 eff. mol/ml ($\times 10^{-12}$)	5·7											6·0
C9 eff. mol/ml ($\times 10^{-12}$)	3·1											1·2

* Normal human serum.

RESULTS

Since on three different occasions no CH50 activity was detectable, the patient's serum was analysed for individual complement components. All complement components tested were found to be within the normal range except C1. The titres and CH50 activity of the parents, two siblings and seven other members of the family (Table 1) were found to be normal except for the paternal grandmother (II-16) who exhibited reduced levels of all complements; she had a history of syphilis many years ago. Since the C1 subcomponent, C1q, binds the C1 macromolecule to sensitized erythrocytes (EA), normal levels of haemolytic active C1 in the sera tested also indicated a normal level of C1q. The absence of C1 activity in the patient serum was found to be due to the lack of C1q as shown immunochemically in Fig. 2. It can be seen that C1q was detectable in the sera of the mother (No. 2), the father (No. 3), as well as of the two brothers (Nos. 5 & 6) with monospecific anti-human C1q (No. 7), whereas no C1q was detectable in the patient serum (Nos 1 & 4) thus confirming the results of the functional tests. Immunochemically, C1s and C1r were detectable and were higher than in control sera. The patient's serum was not anti-complementary when incubated with normal serum in various ratios which showed the absence of an inhibitor.

The CH50 values of the patient became normal 1·5 and 4 hr after plasma infusion; however, the C1 titres were still low, being about 1–3% of those of the control (Table 2).

On another occasion, after one unit of plasma infusion, the kinetics of C1q in the patient's serum were examined functionally. The peak of haemolytic C1q activity was reached after 30 min, after which activity dropped to almost undetectable levels within 24 hr (Fig. 3); the half life was calculated from plotted values on a semilog paper to be 3·4 hr.

The addition of highly purified human C1q to the patient serum restored the C1 activity, indicating the presence of the two other C1 subcomponents, C1r and C1s. The titres of C1r and C1s were found to be about three times higher than in normal human serum (Loos *et al.*, in preparation). Titration of highly purified C1q with patient serum as a source of C1r and C1s resulted in a linear dose-response curve (Berkel *et al.*, 1977).

HLA typing was performed on the patient and nine available members of the family (Fig. 1, Table 3).

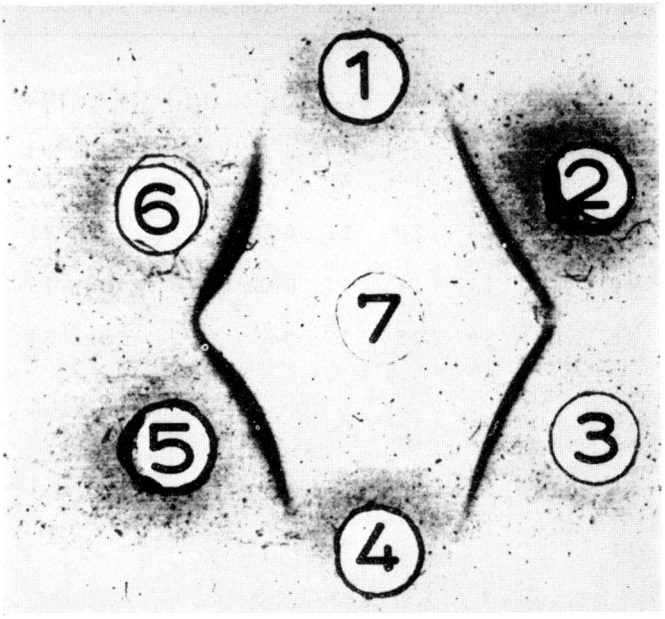

FIG. 2. Immunodiffusion of serum H.I.I. (1 & 4), mother of H.I.I. (2), father of H.I.I. (3) and two brothers of H.I.I. (5 & 6) against a monospecific antiserum to human C1q (7), a subcomponent of the first component of complement.

The patient's mother possessed A10, —/A3, Bw35 and his father had Aw30, B7/A1, B15, antigens. The patient and his 9-year-old brother carried A10, —/Aw30, B7 antigens. His younger brother possessed Aw30, B7/A3, Bw35 antigens. Typing for the D locus antigens was not done as the cell panel was not available. The results of BF typing can be seen in Table 3.

Special studies were performed on post mortem tissues. Light microscopy sections of the skin, muscle and liver did not reveal any pathological changes. In the kidney, a segmental thickening in the glomerular basement membrane (GBM), a mesangial cell proliferation, an increase in mesangial matrix and focal adhesions within the Bowman capsule were seen. A few leucocytes were observed in some glomeruli. There were infrequent dilatations and epithelial atrophy of the tubules, and their lumen contained eosinophilic cylinders. In addition to focal interstitial mononuclear leucocyte infiltration, a minimal fibrosis was present close to some of the glomerular areas (Fig. 4a, b). Immunofluorescence microscopy of the skin revealed a diffuse bright granular capillary wall staining for IgG (++) and C3 (+++) in dermal layers. In the kidney, there was strong diffuse coarse granular staining for IgG (+++), C3 (++++) and IgA (++) on the GBM and mesangium, and also for C3 (++) on small arteriolar walls (Fig. 5a, b). The other antisera conjugates did not give any positive reactions on the kidney or skin.

Under electron microscopy, nearly all glomeruli appeared to lose their normal morphological structure. The most prominent changes were observed along the capillary basal lamina of the glomerulus.

TABLE 2. Haemolytic titres of complement in the patient's serum before and after plasma infusion

	Before plasma	1·5 hr after plasma	4 hr after plasma	NHS (control)
CH50 (u/ml)	0	35·0	34·0	37·5
C1 eff. mol/ml ($\times 10^{-13}$)	0	0·064	0·022	2·0

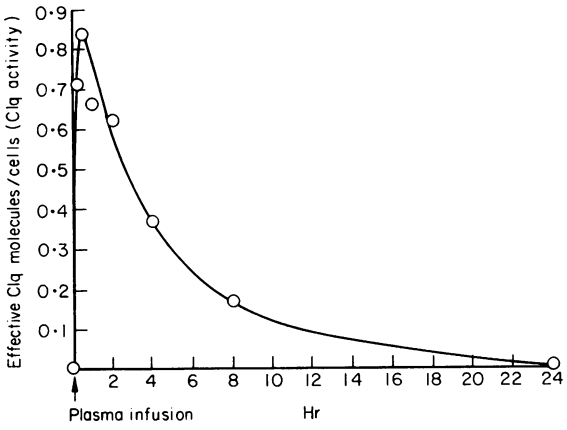

FIG. 3. Kinetics of the detection of C1q in C1-deficient serum after the infusion of 1 unit plasma. The haemolytic assay for C1q is based on the ability of C1q to reconstitute with C1r and C1s forming a haemolytic-effective C1 molecule; therefore, the C1q molecule in the C1 complex formed is an 'effective C1q molecule'.

At several points the visceral epithelial foot-processes had been separated from the basal lamina by large deposits of electron dense material (Fig. 6). These were generally subepithelial, sometimes within the compact central layer of basal lamina, and only occasionally subendothelial. The basal lamina showed local areas of thickening. The size of the deposits was variable. Their fine structure, brought about by fine and coarse granules, also varied, showing different electron densities. Some of the foot-processes surrounding the deposits revealed small aggregates of dense material in their cytoplasm which seemed to be very similar structurally to the deposits.

In general, there was an increase and swelling in the epithelial cells, and a loss of organization in their foot-processes, most of the latter having been fused to each other. There was also an increase in the number of endothelial and mesangial cells most of which showed expansion. The mesangial matrix revealed some increase with a resultant density similar to that of the deposits. With the above findings the pathological diagnosis was compatible with a mesangioproliferative glomerulonephritis.

TABLE 3. The HLA antigens and BF typing

Pedigree No.		Histocompatibility antigen	BF antigen
II-16	(paternal grandmother)	A9, —/Aw30, B7	F
III-8	(maternal grandfather)	Aw30, —/A10,—	FS
III-9	(maternal grandmother)	—, B7/A3, Bw35	FS
IV-3	(aunt)	A10, —/A3, Bw35	S
IV-4	(uncle)	Aw30, —/—, B7	F
IV-11	(mother)	A10, —/A3, Bw35	S
IV-12	(father)	Aw30, B7/A1, B15	F
V-4	(propositus)	A10, —/Aw30, B7	FS
V-5	(brother)	A10, —/Aw30, B7	FS
V-6	(brother)	Aw30, B7/A3, Bw35	FS

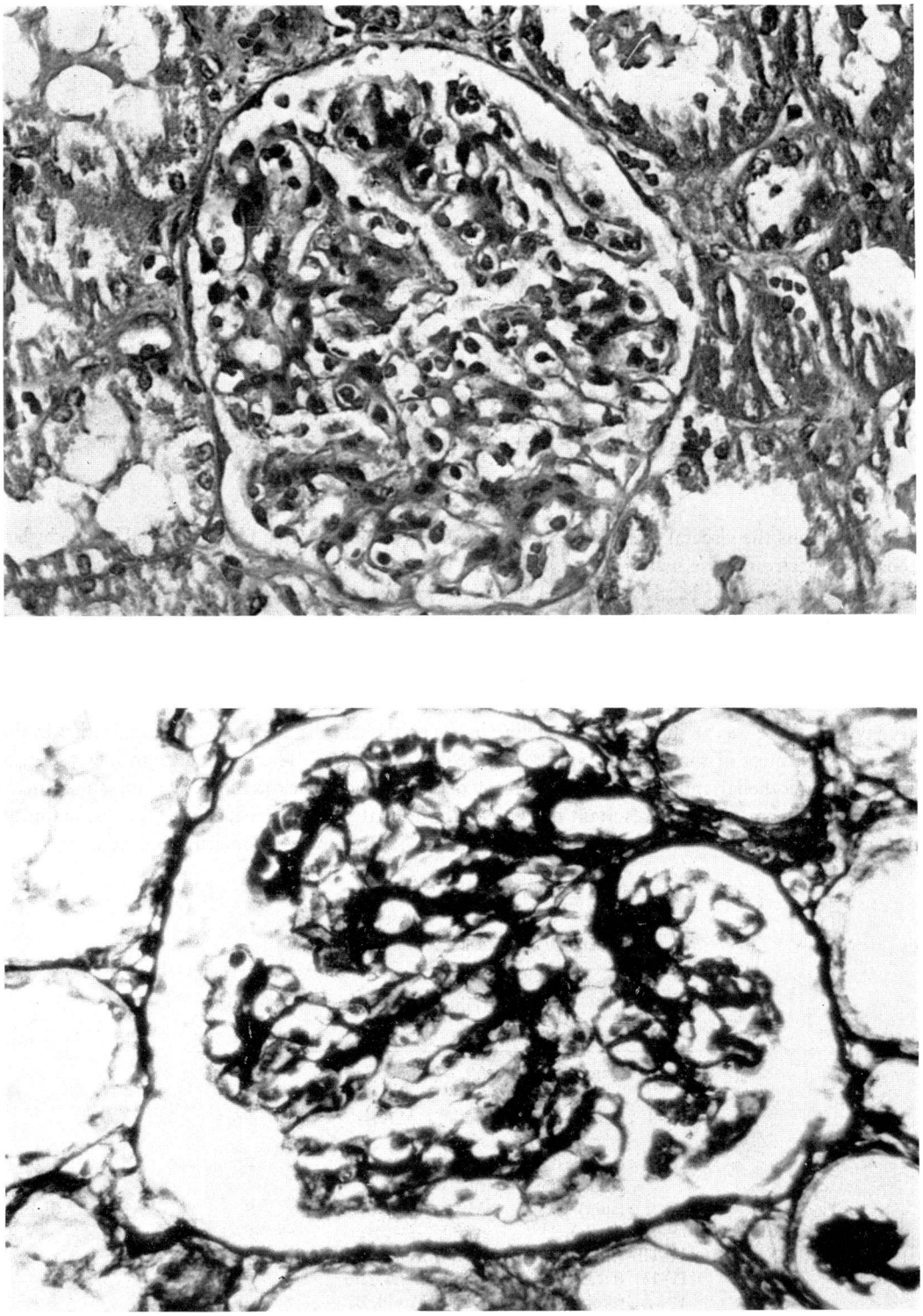

FIG. 4. (a) Mesangial cell proliferation and segmental thickening of glomerular basement membrane (GBM) in a glomerulus (H & E × 500). (b) An increase in the mesangial matrix demonstrated by periodic acid-methanamine silver staining (H & E × 600).

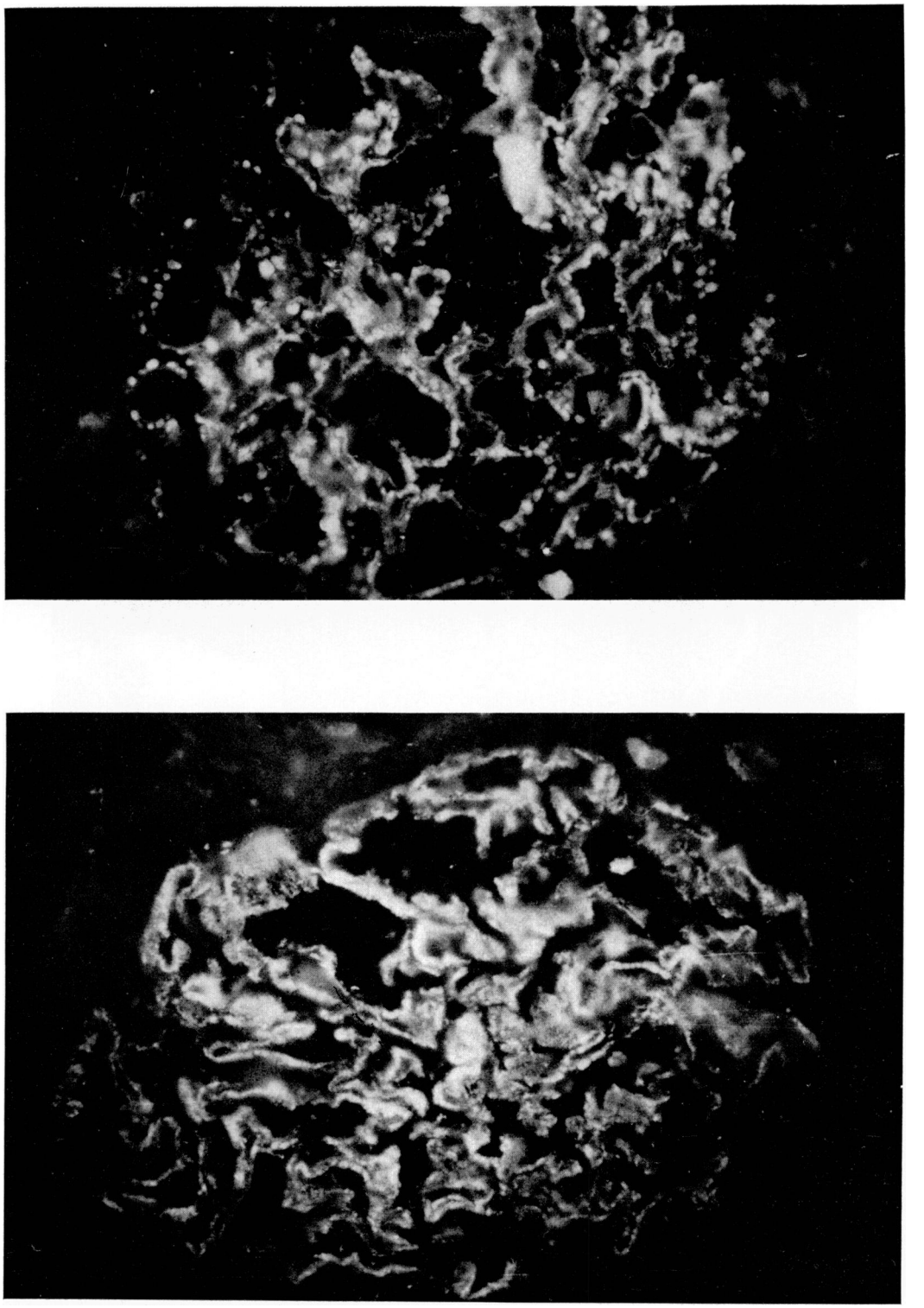

FIG. 5. (a) Diffuse coarse granular staining with FITC-conjugated anti-IgG on GBM (H&E × 600). (b) Bright diffuse coarse granular staining with FITC-conjugated anti-C3 in a glomerulus (H&E × 600).

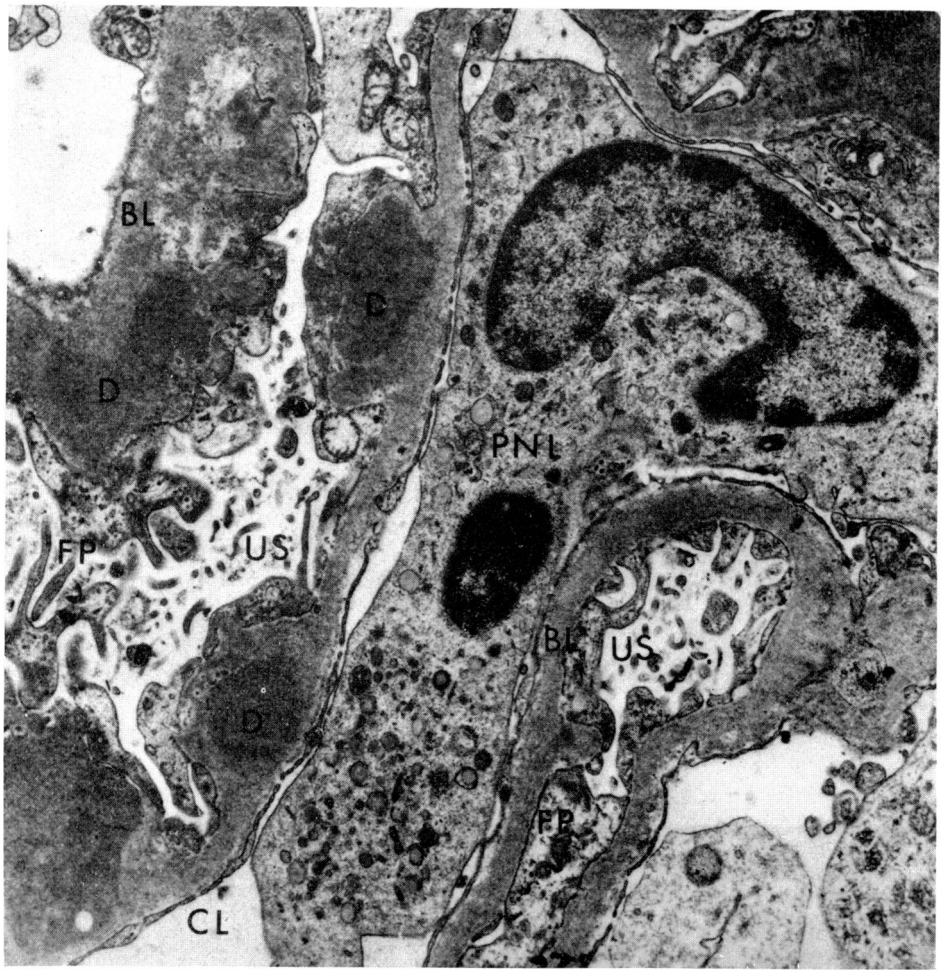

FIG. 6. Electron micrograph of a glomerular capillary loop. Electron dense deposits (D) of different sizes are seen along the basal laminar of the glomerular capillary. Most of them are subepithelial or within the lamina densa. The visceral epithelial foot-processes (FP) have lost their normal structure and organization and show swelling and extensive fusion. CL: Capillary lumen; BL: basal lamina, US: urinary space; PNL: polymorphonuclear leucocyte. (H & E × 14,000.)

DISCUSSION

We have described a patient with recurrent skin lesions and chronic infections of multiple organ systems associated with a deficiency of C1q. Closer analysis of the complement system in the patient and available family members made it clear that the absence of serum haemolytic complement activity was attributable to a complete selective C1q deficiency whereas C1r and C1s were present. Haemolytic C1 activity was reconstituted upon the addition of purified C1q. The administration of fresh frozen plasma restored the haemolytic activity and alleviated the skin lesions temporarily.

So far, the published cases of C1q deficiency have either been associated with severe combined immunodeficiency in the infant age groups (Ballow *et al.*, 1973; O'Connell *et al.*, 1966), or with lupus-like syndromes with varieties of skin lesions or vasculitis (Marder *et al.*, 1976; McDuffie *et al.*, 1973; Sissons *et al.*, 1974; Wara *et al.*, 1975). After the report of Müller-Eberhard & Kunkel (1961) on low C1q levels in some agammaglobulinaemic subjects, further studies showed C1q to be decreased in myeloma, adult common variable hypogammaglobulinaemia and systemic lupus erythematosus (Atkinson

et al., 1978; Kohler & Müller-Eberhard, 1972). In studies of hypogammaglobulinaemic subjects, an increased catabolism and a higher vascular distribution of C1q was observed, indicating that the low C1q levels were not due to impaired synthesis. It was shown that the metabolism of C1q is influenced by the serum IgG concentration, demonstrating a correlation between C1q and the immunoglobulin levels in immunodeficiency diseases (Kohler & Müller-Eberhard, 1972).

In our patient the serum immunoglobulin levels were not decreased and we were not able to demonstrate the presence of myeloma, systemic lupus erythematosus (SLE), other collagen diseases or vasculitis by the various tests performed. Nor did we find any circulating C1q precipitins in the patient's serum as described previously by Agnello *et al.* (1971).

In the patient, anti-smooth muscle antibodies, immune complexes and anti-HBsAg antibody tests were positive. He had deposits of IgG and C3 in the immunofluorescent studies of the skin biopsy. A mesangioproliferative type of glomerulonephritis was found in the studies with light, fluorescent and electron microscopies (Figs 4–6).

In some of the complement deficiency states (C2 and C4), a linkage between the deficient gene and a major histocompatibility complex has been demonstrated (Jersild, Rubinstein & Day, 1976; Ochs *et al.*, 1977). Analysis of the HLA typing in our patient and nine members of the family suggested no such linkage for the gene between C1q deficiency and the HLA antigens. Although the patient's serum had haemolytic (Table 1) as well as immunochemical (Fig. 2) evidence of a selective complete C1q deficiency, we were not able to demonstrate a genetically inherited defect of C1q in this family. The haemolytic activity of C1 which is composed of the subcomponents C1q, C1r and C1s was found to be within the normal range in all members of the family except the paternal grandmother. The paternal grandmother was not available for further studies to explain her reduced levels of complement components which may possibly be secondary to another disease.

The association of systemic lupus erythematosus (SLE) and other collagen diseases has been observed in hereditary deficiencies of complement. C5 deficiency with SLE (Rosenfeld, Kelly & Leddy, 1976), C7 deficiency with Raynaud's phenomenon and scleroderma (Boyer *et al.*, 1975), C8 deficiency with SLE (Jasin, 1976), and many cases of C2 deficiency with SLE or discoid lupus, anaphylactoid purpura, dermatomyositis and chronic vasculitis (Agnello, 1978) have been reported. Membranous glomerulonephritis was found in some of these patients (Agnello, 1978). The exact mechanism for the development of glomerulonephritis in patients with complement deficiency is not known. It is postulated that these patients may have a defective clearance of antigen–antibody complexes by the reticuloendothelial system (RES), because of the failure of opsonization of immune complexes resulting from their complement deficiency (Moncado *et al.*, 1972). A broader hypothesis advocated by Soothill & Steward (1971) and Alpers, Steward & Soothill (1972) is that the development of glomerulonephritis is a reflection of a subtle form of immunodeficiency which is associated with a defective immune elimination of antigen and the formation of immune complexes of a type liable to cause glomerular damage. Another hypothesis proposes that deficiency of the early components of complement predisposes the host to infection by certain organisms involved in the production of connective tissue diseases, in much the same way as the absence of C3 predisposes to specific bacterial infections. The possibility that SLE and other connective tissue diseases have an infectious basis, particularly viral, is a widely held concept (Phillips & Christian, 1969; Schwartz, 1973) and viral-like particles have been described in SLE (Gyorkey *et al.*, 1969). In addition, C-type viral antigens have been found on lymphocytes and in glomerular deposits in patients with SLE (Levis *et al.*, 1974; Mellors & Mellors, 1976). It is possible that with deficiencies of early complement components, the likelihood of proliferation of such an agent may be enhanced and would result in the clinical picture of SLE and other syndromes of connective tissue disease in some individuals (Agnello, de Bracco & Kunkel, 1972). It has been shown that the early components of complement are sufficient for viral neutralization (Daniels *et al.*, 1969; Linscott & Levinson, 1969). Recently, Cooper *et al.* (1976) have shown that antibody-independent lysis of oncornaviruses which occurs with human serum does not occur with C2- or C4-deficient sera. They were also able to show that C1q reacted directly with viral particles. If such agents were involved in the aetiology of SLE, then the marked depression of early complement components in SLE and SLE-related syndromes may indicate a

mechanism of host defence to such organisms or similar ones rather than just a reflection of immune complex formation and disease activity as has been generally thought. Although we have not been able to demonstrate any deposits of C1q in fluorescent microscopy studies using the appropriate antiserum, it is still conceivable that the mechanism suggested above may be responsible from the glomerulonephritis found in our patient.

We believe that any patient presenting with chronic infections and persisting skin lesions should be screened for the presence of a complement component deficiency and our case is a good example of this.

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